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EARLY MIXED CHIMERISM DOES NOT ALTER LONG-TERM PROGNOSIS FOR PATIENTS RECEIVING IV BUSULFAN-FLUDARABINE (IV BU-FLU) WITH ALLOGENEIC STEM CELL TRANSPLANTATION FOR AML/MDS

Tang, X.[1], de Lima, M.[2], Wei, W.[2], Chiattone, A.[2], Thall, P.F.[3], Medeiros, L.J.[4], Rondon, G.[2], Shpall, E.J.[2], Jones, R.B.[2], Nieto, Y.[2], Alousi, A.[2], Champlin, R.E.[2], Andersson, B.S.[2] [1]Jiangsu Institute of Hematology, Soochow, China; [2]UT MD Anderson Cancer Center, Houston, TX; [3]UT MD Anderson Cancer Center, Houston, TX; [4]UT MD Anderson Cancer Center, Houston, TX

Achieving a full versus a mixed chimeric state has been associated with a more favorable outcome after allogeneic stem cell transplantation (allo-SCT) for leukemia. We were intrigued by what appeared to be a high incidence of early (SCT day+30) mixed chimerism, yet a low incidence of serious toxicity and aGvHD, coupled with excellent overall (OS) and disease-free survival (DFS), especially for patients transplanted in remission (CR or CRp), when using the reduced-toxicity IV Bu-Flu regimen described by de Lima et al (BLOOD 2004;104:857-64). We hypothesized that use of a highly sensitive PCR-based chimerism assessment technique, as well as separate assaying of myeloid- and T-cell chimerism, might provide more reliable data for assessing the prognostic value of chimerism for overall (OS) and disease-free survival (DFS) after allo-SCT.

Patients and Methods: Chimerism assay was performed with a PCR-based technique to assess microsatellite polymorphism of informative loci, and multi-variate Cox models including chimerism and other covariates were fit for OS and DFS (Table 1).

Results: 206 AML/MDS patients received Flu at 40 mg/m^2 daily for 4 days, each dose followed by IV Bu, either at 130 mg/m^2 or pharmacokinetically targeted to an average daily systemic exposure of 6,000 μMol-min. There were 108 males and 98 females, median age of 47 years (16-66). Sixty-six were in first CR, 48 in second CR, 18 had 1st refractory relapse, 20 were in 1st or 2nd untreated relapse, 37 had induction failures, and 17 high-risk MDS. One patient died before day +30 and so did not have chimerism studies. The median follow-up of patients still alive is 5.5 yrs (range 1.3 - 8.6); 193 patients who engrafted and were in CR on day +30 had chimerism analyses; 64% were full chimeras, 36% were mixed chimeras (i.e. ≥ 1% host cell DNA). Achieving CR after SCT was important, as was a cytogenetic "high-risk" subgroup (mainly -5/-7, Ph+, or complex chr. abnormalities). However, in the multivariate model neither higher age nor attainment of full vs. mixed donor chimerism by day +30 were of additional predictive value for either OS or DFS.

We conclude that when the reduced-toxicity IV Bu-Flu regimen is used for AML/MDS only cytogenetic subgroup (high-risk/others) and disease state (CR/No CR) but neither patient age nor chimeric state by SCT day +30 were independently predictive of an altered prognosis relative to OS and DFS.

Table 1.

Parameter	β	SE(β)	P-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age (1 yr increase)	0.002	0.009	0.82	1.00	0.99	1.02
D+30 chimerism (yes vs. no)	-6.68	4.94	0.18	0.001	0.00	20.32
D+30 chimerism (magnitude)	0.064	0.050	0.20	1.07	0.97	1.18
Cytog risk (Bad vs. others)	0.42	0.20	0.035	1.52	1.03	2.23
Disease status at Tx (CR/CRp vs. others)	-0.89	0.21	<.0001	0.41	0.27	0.61

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SAFETY AND UTILITY OF LIVER BIOPSY IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS WITH LIVER DYSFUNCTION

Benjamin, H., Costa, R., Tiriveedhi, L., Rossetti, J., Sahovic, E., Lister, J. Western Pennsylvania Cancer Institute, Pittsburgh, PA

Background: Liver disease is a common, often complex complication of allogeneic hematopoietic stem cell transplantation (HSCT) with multi-factorial etiology. Accurate diagnosis is typically made using a combination of clinical, laboratory and radiological data, assisted by a knowledge of risk factors for particular liver disease.

Methods: To evaluate the safety and utility of liver biopsy in this population, we reviewed data of 45 allogeneic HSCT and donor lymphocyte infusion (DLI) recipients who underwent liver biopsy for hepatic dysfunction of unclear etiology from 1995 to 2006. Seven patients had the procedure performed more than once, yielding a total number of 55 studies.

Results: Time to liver biopsy and liver function studies prior to the procedure were analyzed with patient characteristics depicted in the table below. As a result of this procedure, graft versus host disease (GVHD) was confirmed in 23/49 (47%) of suspected cases and sinusoidal obstructive syndrome (SOS) was confirmed in 1/3 (33%) of suspected cases. Similarly, infection and disease relapse were present in only 33% and 29% of suspected cases, respectively. Drug toxicity, however, was confirmed in 12/20 (60%) of suspected cases. The procedure was helpful in modifying or continuing current therapy in 40% of the cases. A total of 13% of the procedures had associated complications including capsular perforation with fatal hemorrhage (n = 2, 4%).

Conclusions: While not without risk, liver biopsy findings confirmed or refuted the clinical diagnosis in 60% of cases. This information was used to modify therapy in 40% of cases. Whether the risk of liver biopsy is justified by the benefit of therapeutic change remains to be demonstrated by further investigation.

Table 1. Patient Characteristics

Patients	n = 45
Mean age (range)	42.8 (20-64)
Sex (M/F)	32/13
Disease	
ALL	4 (9%)
AML	7 (16%)
CML	9 (20%)
Hodgkin's Lymphoma	4 (9%)
Non-Hodgkin's Lymphoma	13 (29%)
MDS	7 (16%)
Multiple Myeloma	1 (2%)

ALL indicates Acute Lymphocytic Leukemia, AML: Acute Myelogenous Leukemia; CML: Chronic Myeloid Leukemia; MDS: Myelodysplastic Syndrome

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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PATIENTS WITH LIGHT RENAL FAILURE

Oshima, K.[1,10], Kanda, Y.[1,10], Nanya, Y.[2,10], Tanaka, M.[3,10], Nakaseko, C.[4,10], Yano, S.[5,10], Fujisawa, S.[6,10], Fujita, H.[7,10], Takahashi, S.[8,10], Kanamori, H.[3,10], Okamoto, S.[9,10] [1]Saitama Medical Center, Jichi Medical University, Saitama, Japan; [2]University of Tokyo, Tokyo, Japan; [3]Kanagawa Cancer Center, Kanagawa, Japan; [4]Chiba University School of Medicine, Chiba, Japan; [5]Jikei University School of Medicine, Tokyo, Japan; [6]Yokohama City University Medical Center, Kanagawa, Japan; [7]Yokohama City University Hospital, Kanagawa, Japan; [8]Advanced Clinical Research Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan; [9]Keio University School of Medicine, Tokyo, Japan; [10]Kanto Study Group for Cell Therapy, Japan

Background: Although renal function may affect the outcome of allogeneic hematopoietic stem cell transplantation (HSCT), mildly reduced renal function which is defined as serum creatinine level between 1.2 to 2.0 mg/dl did not correlate with non-relapse mortality (NRM) in the analysis of hematopoietic cell transplantation comorbidity index (HCT-CI). Creatinine clearance rate (Ccr) is a useful and exact way to asses renal function. Impact of renal function which is evaluated using Ccr before HSCT on the outcome has not been investigated yet.

Purpose: The aim of this study is to assess the outcome of patients with mildly reduced renal function which was defined by Ccr before HSCT.

Method: Patients who underwent allogeneic HSCT using calcineurin inhibiter between January, 2004 and December, 2008 at the seven institutes of Kanto Study Group for Cell Therapy (KSGCT) with an available Ccr data before HSCT were included in this study.